IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Gordon J. Dow et al.	Examiner: San Ming R Hui
Serial No.:	10/800,840	Group Art Unit: 1617
Filed:	March 15, 2004	Docket No.: 2102.010US2
Title:	FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY	

PETITION FOR RETROACTIVE FOREIGN FILING LICENSE UNDER 37 § C.F.R. 5.25

MS L&R
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicants hereby petition under 35 § U.S.C. 184 and 37 § C.F.R. 5.25 for a retroactive foreign filing license for Great Britain Patent Application No. 9823036.0, filed October 22, 1998 ("the GB Patent Application," copy attached), and PCT Application No. PCT/GB99/03472, filed October 20, 1999 ("the PCT Application," copy attached), both of which correspond to U.S. Patent Application Serial No. 10/800,840, now U.S. Patent No. 7,300,669 ("the '669 patent," copy attached).

As described in the accompanying Verified Statement, although the invention was made in the United States, the GB Patent Application was filed abroad in the Great Britain Patent Office, as well as in the GB receiving Office for the PCT application, without obtaining a foreign filing license through error and without deceptive intent. This foreign filing is not considered to be detrimental to the public safety or defense and does not involve any secrecy order or raise any issue of national security for the United States. A foreign filing license was granted with respect to the U.S. Serial No. 10/800,840, subsequent to its filing date of March 15, 2004 (copy attached).

A request is respectfully made for expedited handling. The U.S. Patent and Trademark Office is hereby authorized to charge the petition fee of $200.00.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

GORDON J. DOW ET AL.

By their Representatives,

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Date 12-15-2010

By _____
Warren D. Woessner
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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VERIFIED STATEMENT ACCOMPANYING PETITION FOR RETROACTIVE FOREIGN FILING LICENSE UNDER 37 § C.F.R. 5.25

MS L&R
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Ms. Karen Crawley, hereby declare as follows:

1. This Verified Statement accompanies a Petition made under 35 U.S.C. § 184 and 37 § C.F.R. 5.25 for a retroactive foreign filing license for Great Britain Patent Application No. 9823036.0, filed on October 22, 1998 ("the GB Patent Application"), and PCT Application No. PCT/GB99/03472, filed on October 20, 1999 ("the PCT Application"), which correspond to U.S. Patent Application Serial No. 10/800,840, now U.S. Patent No. 7,300,669 ("the '669 patent").

2. I am a European Patent Attorney and have been employed at Glaxo Wellcome PLC, now GlaxoSmithKline, for 13 years. I was employed at Glaxo Wellcome PLC when the GB Patent Application and the PCT Application were filed.

3. At the time of filing of the GB Patent Application and the PCT Application, it was Glaxo Wellcome PLC practice to file, through its central office in Great Britain, priority patent applications and PCT patent applications at the UK patent office. It was Glaxo Wellcome PLC practice to obtain a foreign filing license from the US Patent Office prior to filing a patent application on a US derived invention in the UK patent office.

4. The subject matter of the '669 patent was invented in the United States by U.S. citizens.

5. Upon a review of our files, both in the U.S. and in Great Britain, we were unable to locate a copy of the foreign filing license granted with respect to the GB Patent Application or the PCT Application.

6. If a foreign filing license was not requested for the GB Patent Application and PCT Application, these were filed abroad in error and without deceptive intent on October 22, 1998 and October 20, 1999, respectively.

7. The subject matter of the GB Patent Application and PCT Application was not under a secrecy order at the time they were filed abroad, and it is not currently under a secrecy order. The filing of the GB Patent Application and PCT Application is not considered to be detrimental to the public safety or defense and does not involve any secrecy order or raise any issue of national security for the United States.

8. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 to Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued therefrom.

Date 15/12/10 By _____
Karen Crawley

PCT/GB99/03472

The Patent Office

INVESTOR IN PEOPLE

GB 99/3472

The Patent Office
Concept House
Cardiff Road
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REC'D 17 NOV 1999
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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

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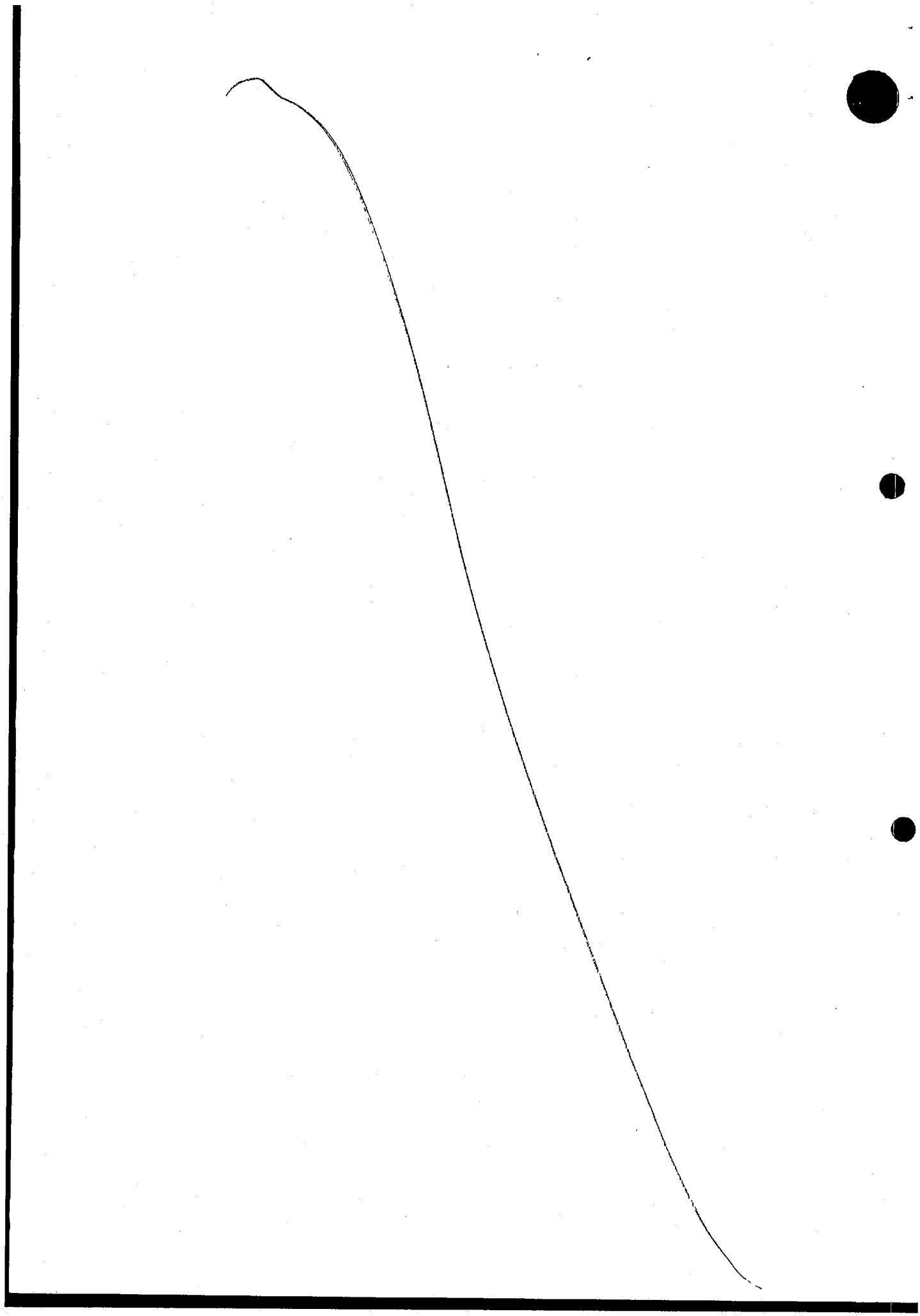
Dated 2 NOV 1999



Patents Form 1/77

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Patents Act 1977
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The Patent Office

THE PATENT OFFICE
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1	Your Reference	KC/PU3556
2	Patent application number *(The Patent office will fill in this part)*	22 OCT 1998 **9823036.0**
3	Full name, address and postcode of the or of each applicant *(underline all surnames)*	GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 0NN
	Patents ADP number *(if you know it)*	03575003
	If the applicant is a corporate body, give the country/state of its corporation	
4	Title of the invention	FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY
5	Name of your agent *(if you know one)*	KAREN CRAWLEY (SEE CONTINUATION SHEET)
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	GLAXO WELLCOME PLC GLAXO WELLCOME HOUSE, BERKELEY AVENUE GREENFORD, MIDDLESEX UB6 ONN, GB
	Patents ADP number *(if you know it)*	7259069001

		Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)
6.	If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

		Number of earlier application	Date of filing (day / month / year)
7	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		

8.	Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	1
Description	13
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10 If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: Karen Crawley 21 October 1998
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

Kim Allen

0181-966 5721

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication of communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the patent Act 1977 stops you from applying for a patent abroad without first getting written permission form the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been received

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If you have answered "Yes" Patents Form 7/77 will need to be filed.

d) *Once you have filled in the form you must remember to sign and date it.*

e) *For details of the fee and ways to pay please contact the Patent Office.*

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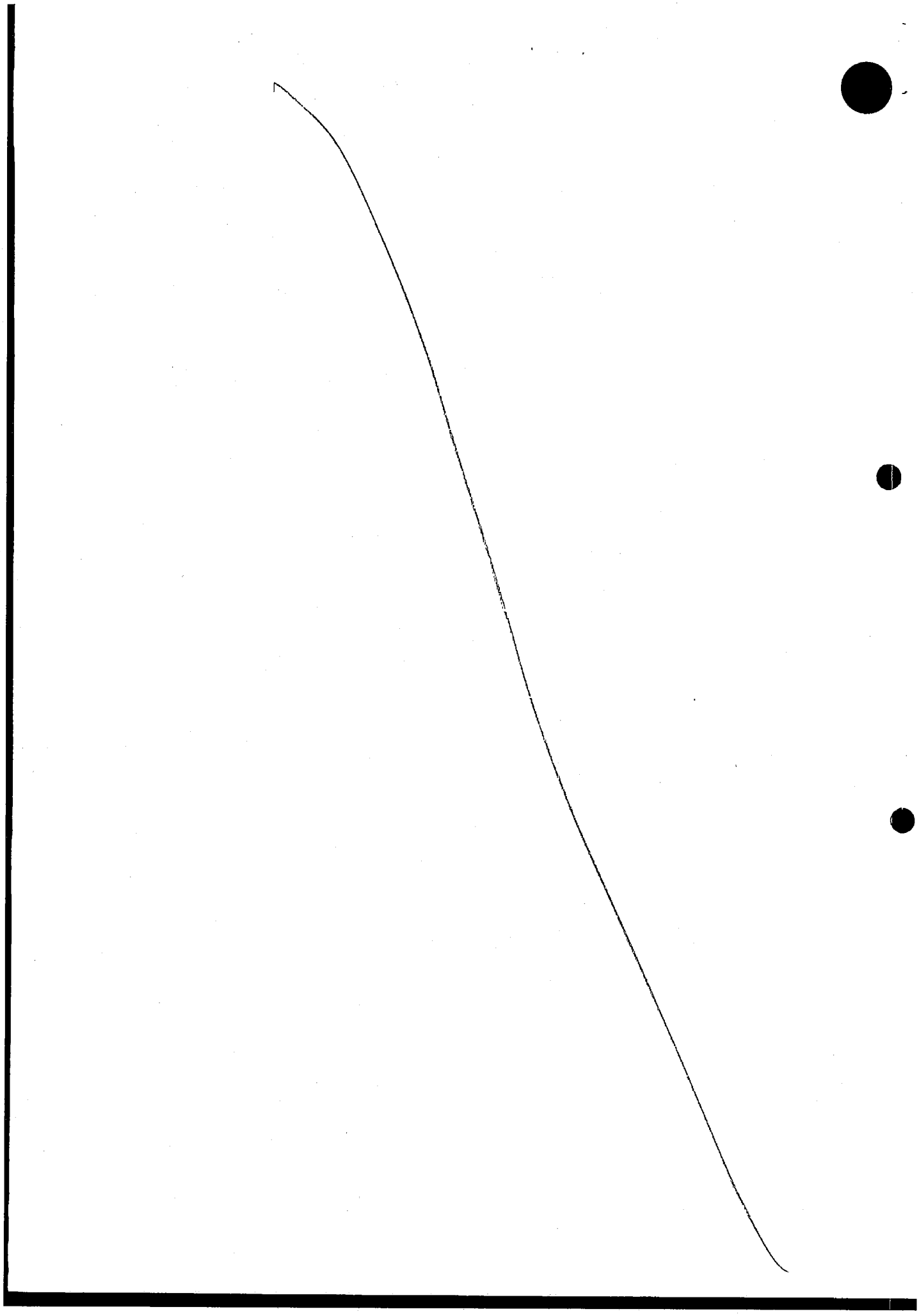

FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

Background of the Invention

Field of the Invention

The present invention is directed to a fluticasone lotion having improved vasoconstrictor activity over a cream formulation. The fluticasone lotion exhibits significant vasoconstrictor potency and excellent anti-inflammatory activity.

Description of Related Art

Fluticasone propionate is a steriod having anti-inflammatory, anti-pruitic, and vasoconstrictive properties.

Fluticasone propionate cream (0.05%) is sold under the tradename Cutivate® cream. Each gram of Cutivate® cream (0.05%) contains 0.5 mg fluticasone propionate in a base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, buffers and preservatives.

Mineral oil is a known occlusive agent. Occlusion in topical drug delivery is known to increase the vasoconstrictor potency of the topical steroid. By increasing the vasoconstrictor potency, the effectiveness of the steroid is increased. Disadvantageously, occlusive agents such as mineral oil can reduce the esthetic appeal of topical formulations as they may impart an undesirable oily feel to the skin. With the removal or significant reduction of the occlusive agent, one of ordinary skill in the art would expect to see a decrease in the vasoconstrictor potency of the steroid, and thus a decrease in the effectiveness of the topical steroid formulation.

Surprisingly, it has been found by the present inventors that the removal of the occlusive agent actually increases the vasoconstrictor potency of fluticasone, and thus, the effectiveness of the steroid. Moreover, a lotion greatly improves the organoleptic feel and spreadability of the drug over a large area, when compared with a cream. The present invention is based on the above finding.

Summary of the Invention

The present invention is directed to a topical fluticasone lotion for the treatment of dermatological disorders. The lotion comprises:

(a) about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;

(b) about 1.0 to about 10.0 wt.% of a C_{14}-C_{20} fatty alcohol, or mixtures thereof;

(c) about 1.0 to about 5.0 wt.% of at least one skin conditioning agent; and

(d) about 5.0 to about 15.0 wt.% of propylene glycol; and up to about 10.0 wt.% mineral oil or soft white paraffin, and the balance being water which can contain additives such as preservatives and buffers.

This invention is also directed to a topical fluticasone lotion which comprises:

(a) fluticasone propionate in an amount of from about 0.005 to about 1.0 wt.%;

(b) a C_{14}- C_{20} fatty alcohol, or mixtures thereof, in an amount of from about 3.0 to about 7.0 wt.%;

(c) at least one skin conditioning agent in an amount of from about 0.5 to about 3.0 wt.%;

(d) a surfactant in an amount of about 0.25 to about 3.0 wt.%;

(e) propylene glycol in an amount of from about 7.0 to 12.0 wt.%; and

(f) up to about 10 wt.% mineral oil or soft white paraffin.

Detailed Description of the Preferred Embodiments

The lotion of the present invention has the added benefit of being chemically and physically stable for at least 6 months at 40°C.

Fluticasone or a pharmaceutically acceptable salt or ester thereof, such as fluticasone proprionate is added to the formulation in an amount of from about 0.005 to about 1.0 wt.% preferably 0.005 to 0.5 wt.%, and most preferably about 0.005 to about 0.1 wt.%.

The C_{14}-C_{20} fatty alcohol or mixtures thereof are added to the formulation as a thickener and stabilizer. Examples include, but are not limited to, cetyl alcohol, stearyl alcohol, and cetostearyl alcohol. The C_{14}-C_{20} fatty alcohol is present in an amount of

from about 1.0 to about 10.0 wt.%, preferably about 3.0 to about 7.0 wt.%, and most preferably about 4.0 to about 6.0 wt.%.

Conventional skin conditioning agents known in the art such as emollient skin conditioning agents can be used in preparing the lotion of the present invention. Skin conditioning agents are defined in the CTFA (Cosmetic Toiletry and Fragrance Association) Cosmetic Ingredient Handbook (2nd ed. 1992) and the Handbook of Pharmaceutical Excipients (2nd ed. 1994). Examples of such skin conditioning agents include, but are not limited to cholesterol, glycerine, glycerol monostearate, isopropyl myristate and palmitate, and lanolin alcohols, or mixtures thereof. Particular examples are isopropyl myristate and cetostearyl alcohol. The skin conditioning agent is added in an amount of from about 1.0 to about 5.0 wt.%, preferably about 1.0 to about 3.0 wt.%, and most preferably about 1.0 to about 2.0 wt.%. In a preferred embodiment, dimethicone is combined with at least one other skin conditioning agent, where the amount of dimethicone present is the formulation up to about 5.0 wt.%, preferably about 0.5 to about 3.0 wt.% and most preferably about 1.0 to about 2.0 wt.% of the formulation.

Conventional surfactants used in the art of topical formulations for forming an oil-in-water emulsion can be used and are not limited. Examples of such surfactants are polyoxyalkene oxides of C_{14}-C_{20} fatty alcohols and polyoxyalkylene sorbitan esters, or mixtures thereof with particular examples being Cetomacrogol® 1000 (Crodor Inc.), Ceteth-20®, Tween® 40 or Brig® 78. The surfactant is added in an amount of about 0.25 to about 3.0 wt.%, preferably about 0.5 to about 2.0 wt.%, and most preferably about 0.75 to about 1.5 wt.%.

Mineral oil or white soft paraffin can be added to the lotion in small amounts to act as a skin conditioner. The lotion may contain no mineral oil or no white soft paraffin at all (0 wt.%) or up to about 10.0 wt.%, particularly up to about 5.0 wt.% and most preferably up to about 2.0 wt.%.

Propylene glycol is added to the lotion formulation in an amount of from about 5.0 to about 15.0 wt.%, preferably about 7.0 to about 12.0 wt.% and most preferably 9.0 to 11.0 wt.%.

The viscosity of the topical lotion is from about 2,000 to about 17,000 cps, preferably about 3,000 to about 13,000 cps, as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.

The pH range of the topical lotion should be from about 4 to 7. Preferred buffers to achieve this range, include, but are not limited to sodium citrate/citric acid, dibasic sodium phosphate/citric acid, and the like.

Preservatives used in the present invention can be any of those conventionally used in the art of topical formulations and preferably the formulation should pass US Pharmacopoeia, British Pharmacopoeia and European Pharmacopoeia standards. Preferred preservatives include, but are not limited to imidurea, methylparaben, propylparaben and the like.

Treatment with the lotion of the present invention is accomplished by applying the lotion to the affected areas to be treated. The treatment regimen is varied from patient to patient and condition to be treated and is usually applied once to twice a day. The lotion of the present invention is used to treat inflammatory and pruritic manifestations of corticosteriod-responsive dermatoses.

The lotion of the present invention is manufactured in a conventional manner by mixing the ingredients at elevated temperatures (such as from 45-80°C) then cooling in order to achieve a smooth, homogeneous oil-in-water emulsion.

The following examples merely illustrate the lotion compositions of the invention and not to be construed as limiting. All weight percentages are weight percentages based on the total weight of the composition.

Examples

Example 1

A topical 0.05 wt.% fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Cetostearyl alcohol, NF	5.00

Isopropyl myristate, NF	1.00
Dimethicone 360, NF	1.00
Cetomacrogol 1000, BP	1.00
Propylene glycol, USP	10.00
Imidurea, NF	0.30
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Citric acid (anhydrous), USP	.05
Sodium citrate, USP	0.08
Purified water, USP	s

Example 2

A topical 0.05 wt.% fluticasone propionate lotion formulation in accordance with the present invention is prepared having the following composition:

	(w/w)
Cetostearyl alcohol, NF	5.25
Isopropyl myristate, NF	2.00
Propylene glycol, USP	0.00
Ceteth-20	0.75
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Citric Acid (anhydrous)	0.05
Dibasic sodium phosphate	0.06
Purified water, USP	qs

Example 3

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	.05
Cetosteoryl Alcohol	5.0
Mineral Oil	3.0

Isopropyl myristate	3.0
Ceteth-20	0.75
Propylene Glycol	0.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	qs

Example 4

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	.05
Cetosteoryl Alcohol	5.25
Mineral Oil	1.0
Isopropyl myristate	1.0
Ceteth-20	0.75
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	qs

Example 5

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	.05
Cetosteoryl Alcohol	5.0
Mineral Oil	10.0
Isopropyl myristate	5.0
Ceteth-20	0.75
Propylene Glycol	10.0

Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	qs

Example 6

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	.05
Cetosteoryl Alcohol	7.0
Isopropyl myristate	2.5
Dimethicone	2.5
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	qs

Example 7

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	.05
Cetosteoryl Alcohol	7.0
Isopropyl myristate	5.0
Dimethicone	2.5
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075

Imidurea	0.30
Water	qs

Example 8

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	.05
Cetosteoryl Alcohol	6.0
Isopropyl myristate	2.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	qs

Example 9

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	.05
Cetosteoryl Alcohol	4.7
Isopropyl myristate	3.75
Dimethicone	3.75
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	qs

Example 10

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	.05
Cetosteoryl Alcohol	2.4
Isopropyl myristate	2.5
Dimethicone	5.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	qs

Example 11

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	.01
Stearyl Alcohol	5.0
Isopropyl myristate	3.0
Dimethicone	3.0
Ceteth-20	0.75
Propylene Glycol	5.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	qs

Example 12

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	.01
Stearyl Alcohol	2.5
Mineral Oil	1.0
Isopropyl myristate	1.0
Dimethicone	1.0
Cetomacrogol 1000	0.5
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	qs

Example 13

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	0.1
Cetyl Alcohol	7.0
Mineral Oil	2.0
Isopropyl myristate	2.0
Dimethicone	2.0
Cetomacrogol 1000	1.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	qs

Example 14

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	0.1
Stearyl Alcohol	7.0
Mineral Oil	2.5
Dimethicone	2.5
Ceteth-20	1.0
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	qs

Example 15

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	0.1
Cetostearyl Alcohol	5.0
Mineral Oil	2.5
Dimethicone	1.0
Tween®40	0.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	qs

Example 16

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	0.1
Stearyl Alcohol	5.25

Mineral Oil	5.0
Brig®78	2.0
Propylene Glycol	5.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	qs

Example 17

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	0.05
Cetyl Alcohol	2.0
Isopropyl myristate	5.0
Cetomacrogol 1000	0.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	qs

Example 18

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

	(w/w)
Fluticasone Propionate	0.05
Cetyl Alcohol	2.5
Dimethicone	5.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	qs

Experimental Method
Vasoconstriction Study

The topical anti-flammatory activity of fluticasone propionate formulations was measured using a vasoconstriction assay (McKenzie and Stoughton, Arch. Dermatol., 86, 608(1962)).

Approximately 0.1 mL of the drug product was placed on a 2 cm^2 area of the volar aspect of each volunteer's forearm. Application sites were protected with a guard to prevent removal or smearing, but were not occluded. After approximately 16 hours of contact, the protective guards were removed and the sites gently washed and dried. Skin vasoconstrictor evaluations were preformed on a 4 point scale (0 [no blanching]-3[marked blanching]) at time points corresponding to 2, 3, 6, 8, and 24 hours after drug removal. The data from this clinical trial were used to calculate the mean blanching response and the area under the curve (AUC) for the blanching Versus time.

The higher the score, mean or area under the curve (AUC), the more topically potent:

Measure*	Lotion Example 1	Lotion Example 2	Cutivate® (Fluticasone proprionate) Cream Comparative Example
AUC	28.4	26.7	21.4
Mean	1.58	1.49	1.22

*Results from 17 volunteers.

The inventive lotions show higher vasoconstriction scores than fluticasone Cream. By looking at the 17 patient data set, the vasoconstriction potency of the inventive lotions over the cream is greater.

It will be apparent to those skilled in the art that many modifications thereof may be made without departing from the spirit and scope of the invention.

We claim:

1. A topical lotion which comprises:

(a) about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;

(b) about 1.0 to about 10.0 wt.% of a C_{14}-C_{20} fatty alcohol or mixtures thereof;

(c) about 1.0 to about 5.0 wt.% of one or more skin conditioning agents;

(d) about 5.0 to about 15.0 wt.% of propylene glycol; and

(e) up to about 10.0 wt.% of mineral oil or white soft paraffin.

2. A topical fluticasone lotion which comprises:

(a) fluticasone propionate in an amount of from about 0.005 to about 1.0 wt.%;

(b) a C_{14}-C_{20} fatty alcohol, or mixtures thereof, in an amount of from about 3.0 to about 7.0 wt.%;

(c) one or more skin conditioning agents in an amount of from about 0.5 to about 3.0 wt.%;

(d) a surfactant in an amount of about 0.25 to about 2.0 wt.%;

(e) propylene glycol in an amount of from about 7.0 to about 12.0 wt.%; and

(f) up to about 10 wt.% of mineral oil or white soft paraffin.

3. The lotion according to claim 1, further comprising up to about 5.0 wt.% dimethicone.

4. The lotion according to claim 2, further comprising up to about 5.0 wt.% dimethicone.

5. The lotion according to claim 1, wherein said pharmaceutically acceptable salt of fluticasone is fluticasone propionate.

6. The lotion according to claim 1, having the formula:

Fluticasone propionate	0.05 wt.%
Cetostearyl alcohol	5.00 wt.%
Isopropyl myristate	1.00 wt.%
Dimethicone 360	1.00 wt.%
Cetomacrogol 1000	1.00 wt.%
Propylene glycol	10.00 wt.%

Imidurea	up to	0.30 wt.%
Methyl paraben	up to	0.20 wt.%
Propyl paraben	up to	0.10 wt.%
Citric acid (anhydrous)		0.05 wt.%
Sodium citrate		0.08 wt.%
Purified water		qs

7. The lotion according to claim 1, having the formula

Fluticasone propionate	0.05 wt.%
Cetostearyl alcohol	5.25 wt.%
Isopropyl myristate	2.00 wt.%
Propylene glycol	10.00 wt.%
Imidurea	0.20 wt.%
Methyl paraben	0.20 wt.%
Propyl paraben	0.10 wt.%
Purified water	qs

8. The lotion according to claim 1, having a viscosity of from about 2,000 to about 17,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.

9. The lotion according to claim 2, having the formula

Cetostearyl alcohol	5.25 wt.%
Isopropyl myristate	2.00 wt.%
Propylene glycol	10.00 wt.%
Imidurea	0.20 wt.%
Methyl paraben	0.20 wt.%
Propyl paraben	0.10 wt.%
Purified water	qs

10. The lotion according to claim 1, having a viscosity of from about 3,000 to about 13,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C

11. The lotion according to claim 2, having a viscosity of from about 3,000 to about 13,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.

12. The lotion according to claim 1, containing no mineral oil or white soft paraffin.

13. The lotion according to claim 2, containing no mineral oil or white soft paraffin.

14. A method of increasing the vasoconstrictor potency of fluticasone which comprises applying to the skin the lotion according to claim 1.

15. A method of increasing the vasoconstrictor potency of fluticasone proprionate which comprises applying to the skin the lotion according to claim 2.

16. Use of the lotion according to claim 1 to increase the vasoconstrictor potency of fluticasone.

17. Use of the lotion according to claim 2 to increase the vasoconstrictor potency of fluticasone proprionate.

18. A process for preparing a lotion according to claim 1, which comprises mixing the ingredients recited in claim 1 at elevated temperature; and then cooking said mixture.

19. A process for preparing a lotion according to claim 1, which comprises mixing the ingredients recited in claim 1 at elevated temperature; and then cooking said mixture.

ABSTRACT OF THE DISCLOSURE

The present invention is directed to a fluticasone lotion having improved vasoconstrictor activity. The fluticasone lotion exhibits high vasoconstrictor potency and excellent anti-inflammatory activity.

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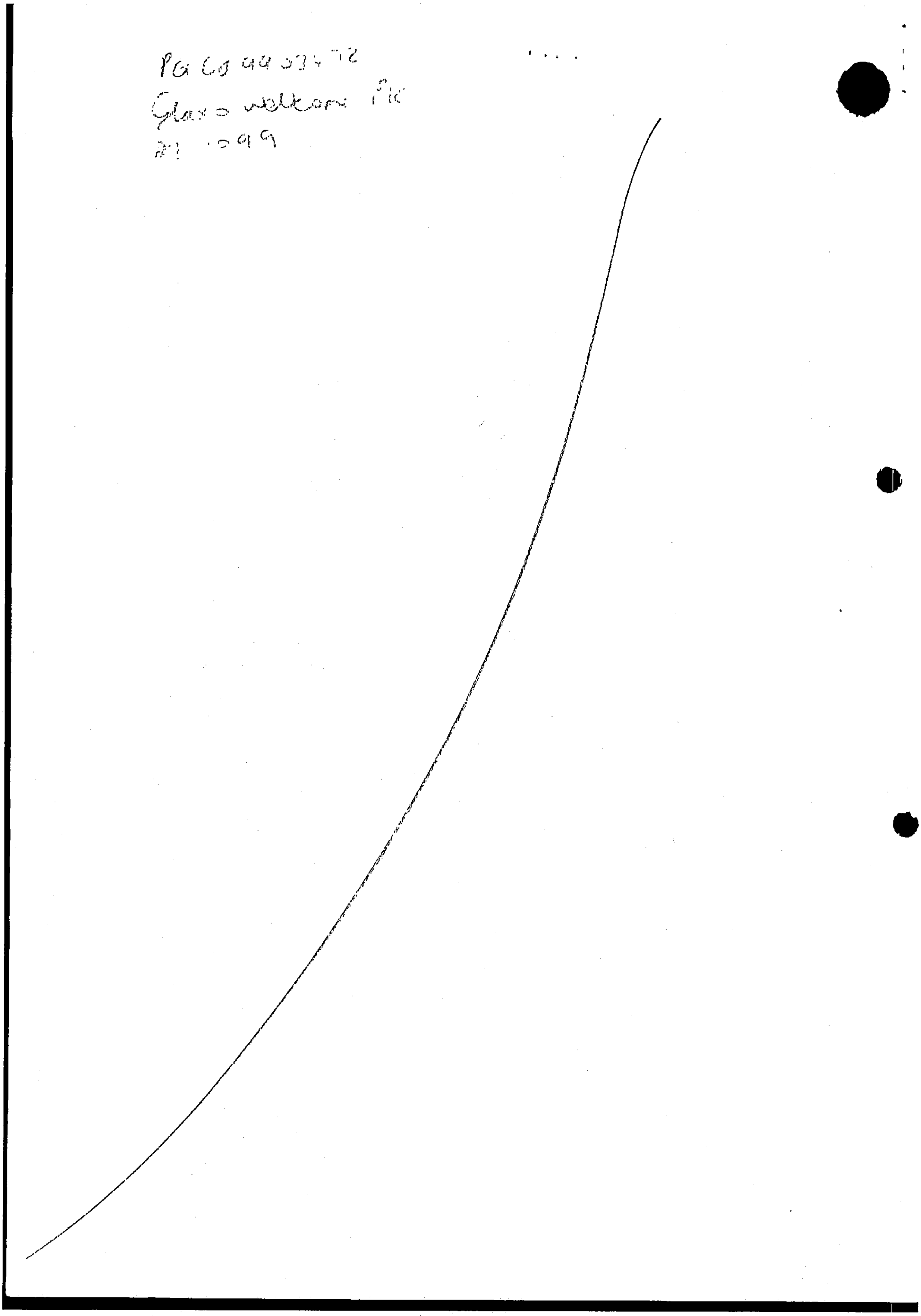

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(54) Title: FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

(57) Abstract

A fluticasone lotion having improved vasoconstrictor and anti-inflammatory activity and higher than expected potency. The fluticasone lotion contains 0.05 weight percent fluticasone propionate and an oil-in-water vehicle that includes excipients. The fluticasone lotion is unexpectedly efficacious while exhibiting an improved safety profile.

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FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

FIELD OF THE INVENTION

The present invention is generally directed to a lotion comprising fluticasone.

BACKGROUND OF THE INVENTION

Fluticasone propionate is a steroid having anti-inflammatory, anti-pruitic, and vasoconstrictive properties. Fluticasone propionate cream (0.05%) is sold under the tradename CUTIVATE® cream. Each gram of CUTIVATE® cream (0.05%) contains 0.5 mg fluticasone propionate in a base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, buffers and preservatives.

Mineral oil is a known occlusive agent. Occlusion in topical drug delivery is known to increase the vasoconstrictor potency of the topical steroid. By increasing the vasoconstrictor potency, the effectiveness of the steroid is increased. However, occlusive agents such as mineral oil can reduce the aesthetic appeal of topical formulations as they may impart an undesirable oily feel to the skin. By removing or significantly reducing the concentration of the occlusive agent, a decrease in the vasoconstrictor potency of the steroid would be expected. Thus, the effectiveness of the topical steroid formulation would be decreased.

The present fluticasone lotion invention unexpectedly shows increased vasoconstrictor potency of fluticasone at decreased concentrations of occlusive agent, thus increasing the steroid effectiveness. The instant fluticasone lotion also significantly improves the organoleptic feel and spreadability of the drug over a large area as compared to a cream. Specifically, the instant fluticasone lotion has improved vasoconstrictor activity over fluticasone cream formulations. The fluticasone lotion is systemically safe and exhibits significant vasoconstrictor potency and efficacy and excellent anti-inflammatory activity.

SUMMARY OF THE INVENTION

One aspect of the invention is a topical lotion comprising about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; a thickening effective concentration of at least one thickener; a conditioning effective concentration of at least one skin conditioning agent; and, an emulsifying effective amount of a surfactant. Unless indicated otherwise herein, all percentages are in terms of weight percent (i.e., w/w, wt.%, etc.). Unless indicated otherwise herein, the term "about" is intended to include values, e.g., weight percents, proximate to the recited range that are equivalent in terms of the functionality of the individual ingredient, the composition or the invention. In addition, unless indicated otherwise herein, a recited range (e.g., weight percents or carbon groups) includes each specific value or identity within the range.

Another aspect of the present invention is a topical fluticasone lotion for the treatment of skin conditions (i.e., dermatological disorders). The lotion comprises about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to 10.0 wt.% of a C_{14}-C_{20} fatty alcohol, or mixtures thereof; about 1.0 to 5.0 wt.% of at least one skin conditioning agent; about 5.0 to 15.0 wt.% of propylene glycol; up to about 10.0 wt.% mineral oil or soft white paraffin, and the balance being water. The lotion optionally contains additives such as preservatives and buffers.

Another aspect of the invention is a topical fluticasone lotion comprising fluticasone propionate in an amount of from about 0.005 to 1.0 wt.%; a C_{14}- C_{20} fatty alcohol, or mixtures thereof, in an amount of from about 3.0 to 7.0 wt.%; at least one skin conditioning agent in an amount of from about 0.5 to 3.0 wt.%; at least one surfactant in an amount of about 0.25 to 3.0 wt.%; propylene glycol in an amount of from about 7.0 to 12.0 wt.%; up to about 10 wt.% mineral oil or soft white paraffin; and the balance in water, preferably purified water, USP.

Yet another aspect of the invention is a method of treating a skin condition. A skin condition (or dermatological disorder) includes, but is not limited to, corticosteroid-responsive dermatosis, atropic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting and pruritis. The method comprises the

steps or acts of providing a lotion including about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to 10.0 wt.% of a C_{14}-C_{20} fatty alcohol or mixtures thereof; about 1.0 to 5.0 wt.% of one or more skin conditioning agents; about 5.0 to 15.0 wt.% of propylene glycol; up to about 10.0 wt.% of mineral oil or white soft paraffin, and the balance in purified water; and, applying the lotion to the skin having the skin condition. Preferably, the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5. The lotion of the present invention has the added benefit of being chemically and physically stable for at least 6 months at 40°C.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Fluticasone or a pharmaceutically acceptable salt or ester thereof, preferably fluticasone proprionate, is present in the formulation in a concentration of from about 0.005 to 1.0 wt.% preferably 0.005 to 0.5 wt.%, and more preferably about 0.005 to about 0.1 wt.%. The C_{14}-C_{20} fatty alcohol or mixtures thereof are present in the formulation as a thickener and/or stabilizer. Examples include, but are not limited to, cetyl alcohol, stearyl alcohol, and cetostearyl alcohol. The C_{14}-C_{20} fatty alcohol is present in a concentration in the range of from about 1.0 to 10.0 wt.%, preferably about 3.0 to 7.0 wt.%, and more preferably about 4.0 to 6.0 wt.%.

Conventional skin conditioning agents, such as emollient skin conditioning agents, may be present in the lotion of the present invention. Skin conditioning agents are defined in the CTFA (Cosmetic Toiletry and Fragrance Association) Cosmetic Ingredient Handbook (2nd ed. 1992) and the Handbook of Pharmaceutical Excipients (2nd ed. 1994). Preferred examples of such skin conditioning agents include, but are not limited to, cholesterol, glycerine, glycerol monostearate, isopropyl myristate and palmitate, and lanolin alcohols, or mixtures thereof. Particular examples are isopropyl myristate and cetostearyl alcohol. The skin conditioning agent is present in a concentration in the range of from about 1.0 to 5.0 wt.%, preferably about 1.0 to 3.0 wt.%, and more preferably about 1.0 to 2.0 wt.%. In a preferred embodiment, dimethicone is employed in connection with at least one skin conditioning agent. The concentration of dimethicone in the formulation may be up to about 5.0 wt.%, preferably about 0.5 to 3.0 wt.% and more preferably about 1.0 to 2.0 wt.% of the lotion composition.

At least one conventional surfactants may be used in topical formulations to form the oil-in-water emulsion lotion of the present invention. For example, the surfactants may include, but are not limited to, polyoxyalkene oxides of C_{14}-C_{20} fatty alcohols and polyoxyalkylene sorbitan esters, or mixtures thereof. Preferred surfactants include CETOMACROGOL® 1000 (Crodor Inc.), CETETH-20®, TWEEN® 40 or BRIG® 78. The surfactant may be present in a concentration in the range of about 0.25 to 3.0 wt.%, preferably about 0.5 to 2.0 wt.%, and more preferably about 0.75 to 1.5 wt.%.

Optionally, mineral oil or white soft paraffin are incorporated into the lotion in relatively small amounts to act as a skin conditioner. The lotion may also be free of mineral oil and/or white soft paraffin or contain up to about 10.0 wt.%. The lotion may also contain up to about 5.0 wt.% or up to about 2.0 wt.% skin conditioner.

Propylene glycol may be present in the lotion formulation in a concentration of from about 5.0 to 15.0 wt.%, preferably about 7.0 to 12.0 wt.% and more preferably 9.0 to 11.0 wt.%.

The viscosity of the fluticasone lotion may be in the range of about 2,000 to 17,000 centipoise (cps), and preferably about 3,000 to 13,000 cps, as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.

The pH range of the topical fluticasone lotion may be in the range of about 4 to 7. Conventional buffers may be employed in the lotion formulation to achieve the pH range. The buffers include, but are not limited to, sodium citrate/citric acid, dibasic sodium phosphate/citric acid, and the like.

Optionally, conventional preservatives may be used in the present invention. Preferably, preservatives employed in the formulation should pass US Pharmacopoeia, British Pharmacopoeia and European Pharmacopoeia standards. Preferred preservatives include, but are not limited to, imidurea, methylparaben, propylparaben and the like, and combinations thereof.

Treatment of skin conditions with the lotion of the present invention is accomplished by applying the lotion to the affected areas to be treated. The treatment regimen is varied

from patient to patient and condition to condition. In general, the fluticasone lotion is to be applied once or twice a day to a treatment area. Preferably, the lotion of the present invention is used to treat atopic dermatitis, inflammatory and pruritic manifestations and corticosteroid-responsive dermatoses.

The lotion of the present invention is manufactured in a conventional manner by mixing the ingredients at elevated temperatures (such as from 45-80°C) and then cooling the mixture to achieve a smooth, homogeneous oil-in-water emulsion.

The following examples merely illustrate the lotion compositions of the invention and are not to be construed as limiting the scope of the invention. Unless indicated otherwise, all weight percentages are based on the total weight of the composition.

EXAMPLES

Example 1

A topical 0.05 wt.% fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Cetostearyl alcohol, NF	5.00
Isopropyl myristate, NF	1.00
Dimethicone 360, NF	1.00
Cetomacrogol 1000, BP	1.00
Propylene glycol, USP	10.00
Imidurea, NF	0.30
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Citric acid (anhydrous), USP	0.05
Sodium citrate, USP	0.08
Purified water, USP	balance

Example 2

A topical 0.05 wt.% fluticasone propionate lotion formulation in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Cetostearyl alcohol, NF	5.25
Isopropyl myristate, NF	2.00
Propylene glycol, USP	0.00
Ceteth-20	0.75
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Citric Acid (anhydrous)	0.05
Dibasic sodium phosphate	0.06
Purified water, USP	balance

Example 3

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.0
Mineral Oil	3.0
Isopropyl myristate	3.0
Ceteth-20	0.75
Propylene Glycol	0.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 4

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.25
Mineral Oil	1.0
Isopropyl myristate	1.0
Ceteth-20	0.75
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 5

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.0
Mineral Oil	10.0
Isopropyl myristate	5.0
Ceteth-20	0.75
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 6

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	7.0
Isopropyl myristate	2.5
Dimethicone	2.5
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 7

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	7.0
Isopropyl myristate	5.0
Dimethicone	2.5
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 8

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	6.0
Isopropyl myristate	2.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 9

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	4.7
Isopropyl myristate	3.75
Dimethicone	3.75
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 10

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	2.4
Isopropyl myristate	2.5
Dimethicone	5.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 11

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.01
Stearyl Alcohol	5.0
Isopropyl myristate	3.0
Dimethicone	3.0
Ceteth-20	0.75
Propylene Glycol	5.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 12

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.01
Stearyl Alcohol	2.5
Mineral Oil	1.0
Isopropyl myristate	1.0
Dimethicone	1.0
Cetomacrogol 1000	0.5
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 13

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.1
Cetyl Alcohol	7.0
Mineral Oil	2.0
Isopropyl myristate	2.0
Dimethicone	2.0
Cetomacrogol 1000	1.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 14

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.1
Stearyl Alcohol	7.0
Mineral Oil	2.5
Dimethicone	2.5
Ceteth-20	1.0
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 15

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.1
Cetostearyl Alcohol	5.0
Mineral Oil	2.5
Dimethicone	1.0
Tween®40	0.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 16

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.1
Stearyl Alcohol	5.25
Mineral Oil	5.0
Brig®78	2.0
Propylene Glycol	5.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 17

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetyl Alcohol	2.0
Isopropyl myristate	5.0
Cetomacrogol 1000	0.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 18

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetyl Alcohol	2.5
Dimethicone	5.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

The topical anti-inflammatory activity of fluticasone propionate formulations was measured using a vasoconstriction assay (McKenzie and Stoughton, Arch. Dermatol., 86, 608(1962)).

Approximately 0.1 mL of the drug product of Examples 1-18 were placed on a 2 cm^2 area of the volar aspect of each volunteer's forearm. Application sites were protected with a guard to prevent removal or smearing. The application sites were not occluded. After approximately 16 hours of contact, the protective guards were removed and the sites gently washed and dried.

Skin vasoconstrictor evaluations were preformed on a 4 point scale (0 [no blanching]-3[marked blanching]) at time points corresponding to 2, 3, 6, 8, and 24 hours after drug removal. The data were used to calculate the mean blanching response and the area under the curve (AUC) for the blanching versus time. The higher the score, mean or area under the curve (AUC), the more topically potent. The results are tabulated in Table 1.

Table 1

Measure*	Lotion Example 1	Lotion Example 2	CUTIVATE® (Fluticasone proprionate) Cream Comparative Example
AUC	28.4	26.7	21.4
Mean	1.58	1.49	1.22

*Results from 17 volunteers.

The fluticasone lotions of the present invention show higher vasoconstriction scores than fluticasone cream. As shown by the 17 patient data set, the vasoconstriction potency of the fluticasone lotions is greater than the cream.

The fluticasone lotion of the present invention has proven to be unexpectedly superior in terms of efficacy and safety. Evaluations were performed using the Vasoconstrictor Assay. Evaluations also used a human model to predict clinical potency of corticosteroids in (1) controlled efficacy and safety trials and (2) subjects with a corticosteroid-responsive dermatosis, atopic dermatitis. Safety and efficacy evaluations were performed on the fluticasone lotion 0.05% by applying the lotion extensively to all body regions: head and neck (including face), trunk, upper limbs and lower limbs.

The potency of the fluticasone lotion, as determined by the Vasoconstrictor Assay, was greater than mid-potency fluticasone cream (CUTIVATE™ Cream). The potency of the fluticasone lotion was less than the high-potency corticosteroid preparations. Application of the lotion formulation over 4 weeks resulted in a superior adverse event profile devoid of commonly encountered side effects encountered using corticosteroids in the mid-to-high potency range.

The instant fluticasone lotion was assessed in view of projected efficacy outcomes from the Vasoconstrictor Assay (VC Assay) in humans and corroborated by efficacy outcomes in multicenter vehicle-controlled clinical trials. It was highly desirable for the lotion formulation to show both systemic (adrenal axis suppression) and local (atrophogenic) responses to corticosteroids. The fluticasone lotion was unexpectedly

superior in both categories, and particularly superior in that no atrophy was observed (based on associated signs) even in the more susceptible region (i.e., the face, head and neck).

The Vasoconstrictor Assay (VC Assay; McKenzie and Stoughton) is a standard dermatological assay used to predict the potency of corticosteroid formulations. Potency is related to both side effect potential and efficacy in the treatment of mild to severe dermatoses. Reactions of particular concern include skin thinning (atrophy, including telangectasia), and adrenal axis suppression, which can occur more often (1) under occlusions or (2) when higher potency corticosteroids are employed.

In the VC assay, fluticasone lotion 0.05% was compared to low-potency (HYTONE™ Lotion), mid-potency (CUTIVATE™ Cream; and fluticasone cream 0.05%) and high-potency (TEMOVATE™ Cream; ELOCON™ Lotion). Potency was estimated for two subject populations (Intent to Treat and Positive responders) and includes 3 outcome assessments: 2-hour mean blanching score, are under the time-blanching score curve (AUC) and Average mean blanching from 5 timepoints. The results from the "responder" population is summarised in Table 2.

Table 2

Treatment	Potency	Responder Population		
		2 hour score	AUC	Avg. mean blanching
TEMOVATE™	High	2.7	36.6	2.0
ELOCON™	High	2.2	33.4	1.8
Fluticasone lotion (0.05%)	Mid to High	2.1	26.7	1.5
CUTIVATE™ Cream	Mid	1.8	21.4	1.2
HYTONE™ Lotion	Low	0.8	9.5	0.6

The results show that the fluticasone lotion of the present invention has an unexpectedly high potency for a lotion-based composition.

In addition, as shown in Table 3, criticality for the presence of fluticasone in the lotion of the present invention was established by the comparison between applying the vehicle alone (the fluticasone lotion minus the fluticasone propionate) and the fluticasone lotion. The FPL10005, FPL3003 and FPL30004 studies used the following fluticasone 0.05% lotion formulation.

Ingredient	(wt.%)
fluticasone propionate (micronized)	0.05
cetostearyl alcohol, NF	5.0
isopropyl myristate, NF	1.0
dimethicone 360, NF	1.0
polyoxyethylene (20) cetostearyl ether, NF	1.0
propylene glycol, USP	10.0
imidurea, NF	0.14
methylparaben, NF	0.17
propylparaben, NF	0.06
citric acid (hydrous), USP	0.05
sodium citrate, USP	0.08
purified water, USP	balance (also QSAD)

Table 3

Study	Diagnosis	Application	No. subjects	Outcome Good to cleared(%)
FPL30003	Atopic Dermatitis	QD for up to 4 weeks	FPL (110) Veh. (110)	FPL (78%)* Veh. (33%)
FPL30004	Atopic Dermatitis	QD for up to 4 weeks	FPL (111) Veh. (107)	FPL (68%)* Veh. (28%)

* subjects showing > 50% clearing of lesions

"Veh." is vehicle only formulation

The data of Table 3 show that the fluticasone lotion is more than twice as effective as the vehicle. In a once-a-day application, the differences (%) between the vehicle-only and the fluticasone lotion are 40% and 45% (FPL30004 and FPL30003, respectively). The advantage of the fluticasone propionate lotion over the vehicle control was unexpectedly superior. It is worth noting that the fluticasone lotion application rate was half the preferred application rate of twice per day.

Systemic safety of fluticasone lotion (study FPL10005) was assessed utilising the measurement of adrenal responsiveness to a challenge of cosyntropin ($ACTH_{1-29}$) and measuring the plasma levels of cortisol both before and 30 minutes after ACTH challenge. HPA axis was considered suppressed if the cortisol response to the challenge was less than 18 ug/dL. These studies were conducted in paediatric populations from 3 months to 5 years of age. Because children have a high ratio of body mass to surface, that population is considered to be more at risk than adults.

In these studies fluticasone formulations were tested following a 3 or 4 week course of twice daily application of the fluticasone lotion to at least 35% of the body surface area in subjects with moderate to severe eczema. The results are summarised in Table 4.

Table 4

Cortisol responses - plasma levels =18 ug/dL indicate suppression

Study	Preparation	Adrenal Responsiveness, #suppressed/total
FPL10005	Lotion	0 / 42

These data show that the fluticasone lotion did not suppress the adrenal responsiveness to ACTH stimulation. CUTIVATE™ lotion produced low adrenal suppression as evaluated by the cosyntropin ($ACTH_{1-29}$) stimulation test in paediatric subjects. This age group would be expected to be the most susceptible to side effects of corticosteroids. No adrenal suppression was noted for CUTIVATE™ lotion. These results were unexpectedly superior based on potency estimates from the VC Assay.

Treating skin diseases with topical corticosteroids is of particular concern where the skin is thin (e.g., the face) due to the potential atrophy side effect. Skin atrophy and atrophy-associated signs (such as telangectasia) were monitored in safety studies (HPA Axis Suppression) and efficacy (multicenter pivotal trials). The fluticasone lotion showed no atrophy-associated changes (see Table 4). In addition, atrophogenic potential was assessed in two large multicenter trials (FPL30003, N= 110 treated with fluticasone); FPL30004; N= 111 treated with fluticasone). The subjects had moderate-to-severe atopic dermatitis. After once daily administration for up to 4 weeks, no atrophy or associated signs were ascribed to drug treatment.

Based on the observed outcomes in the VC Assay (used to predict clinical potency), it was expected (1) that the therapeutic benefit would be only slightly more than that for CUTIVATE™ Cream and (2) that the side effects would reflect those observed for CUTIVATE™ Cream. The results were unexpected in that the lotion formulation was more effective than, and superior to, the cream. At half the application rate of fluticasone lotion, a lack of side effects were observed. That observation was unexpected since application of steroids of similar potency typically cause some side effects. As noted herein for the lotion, the lack of both systemic (HPA Axis suppression) and local side effects, even to sensitive areas such as the face (head and neck region) was unexpected.

It will be apparent to those skilled in the art that many modifications and equivalents thereof may be made without departing from the spirit and scope of the invention as set forth in the appended claims.

We claim:

1. A topical lotion comprising:
about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;
about 1.0 to 10.0 wt.% of a C_{14}-C_{20} fatty alcohol or mixtures thereof;
about 1.0 to 5.0 wt.% of at least one skin conditioning agent;
about 5.0 to 15.0 wt.% propylene glycol;
up to about 10.0 wt.% mineral oil or white soft paraffin; and
the balance in water.

2. A topical lotion comprising:
about 0.005 to 1.0 wt.% fluticasone propionate;
about 3.0 to 7.0 wt.% of a C_{14}-C_{20} fatty alcohol, or mixtures thereof;
about 0.5 to 3.0 wt.% of at least one skin conditioning agent;
about 0.25 to 2.0 wt.% of at least one surfactant;
about 7.0 to 12.0 wt.% propylene glycol;
up to about 10 wt.% of mineral oil or white soft paraffin; and
the balance in water.

3. The lotion according to claim 1, further comprising less than about 5.0 wt.% dimethicone.

4. The lotion according to claim 2, further comprising less than about 5.0 wt.% dimethicone.

5. The lotion according to claim 1, wherein said pharmaceutically acceptable ester of fluticasone is fluticasone propionate.

6. The lotion according to claim 1, comprising:
about 0.05 wt.% fluticasone propionate,
about 5.0 wt.% cetostearyl alcohol,
about 1.0 wt.% isopropyl myristate,
about 1.0 wt.% dimethicone,
about 1.0 wt.% cetomacrogol,

about 10.0 wt.% propylene glycol
less than about 0.30 wt.% imidurea,
less than about 0.20 wt.% methyl paraben,
less than about 0.10 wt.% propyl paraben,
about 0.05 wt.% citric acid (anhydrous),
about 0.08 wt.% sodium citrate, and
the balance in purified water.

7. The lotion according to claim 1, comprising:
about 0.05 wt.% fluticasone propionate,
about 5.25 wt.% cetostearyl alcohol,
about 2.0 wt.% isopropyl myristate,
about 10.0 wt.% propylene glycol,
about 0.20 wt.% imidurea,
about 0.20 wt.% methyl paraben,
about 0.10 wt.% propyl paraben, and
the balance in purified water.

8. The lotion according to claim 1, having a viscosity of about 2,000 to 17,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.

9. The lotion according to claim 2, having the formula
about 5.25 wt.% cetostearyl alcohol,
about 2.0 wt.% isopropyl myristate,
about 10.0 wt.% propylene glycol,
about 0.20 wt.% imidurea,
about 0.20 wt.% methyl paraben,
about 0.10 wt.% propyl paraben, and
the balance in purified water.

10. The lotion according to claim 1, having a viscosity of from about 3,000 to 13,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C

11. The lotion according to claim 2, having a viscosity of from about 3,000 to 13,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.

12. The lotion according to claim 1, free of mineral oil or white soft paraffin.

13. The lotion according to claim 2, free of mineral oil or white soft paraffin.

14. Use of the lotion according to claim 1 to increase the vasoconstrictor potency of fluticasone.

15. Use of the lotion according to claim 2 to increase the vasoconstrictor potency of fluticasone proprionate.

16. A process for preparing a lotion according to claim 1, comprising:
mixing the ingredients recited in claim 1 at an elevated temperature; and
cooling said mixture.

17. A process for preparing a lotion according to claim 1, comprising:
mixing the ingredients recited in claim 1 at an elevated temperature; and
heating said mixture.

18. A topical lotion comprising:
about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;
a thickening effective concentration of at least one thickener;
a conditioning effective concentration of at least one skin conditioning agent;
an emulsifying effective amount of a surfactant, and
the balance in water.

19. The lotion of claim 18, wherein the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5.

20. The lotion of claim 18, wherein the lotion is chemically and physically stable for at least 6 months at 40°C.

21. A method of treating a skin condition comprising:
providing a lotion including about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to about 10.0 wt.% of a C_{14}-C_{20} fatty alcohol or mixtures thereof; about 1.0 to about 5.0 wt.% of at least one skin conditioning agents; about 5.0 to about 15.0 wt.% of propylene glycol; less than about 10.0 wt.% of mineral oil or white soft paraffin, and the balance in water; and,
applying the lotion to the skin having the skin condition.

22. The method of claim 21, wherein the skin condition is corticosteroid-responsive dermatosis, atopic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting or pruritis.

23. The topical lotion of claim 21, wherein the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5.

24. The lotion of claim 21, wherein the lotion is chemically and physically stable for at least 6 months at 40°C.

INTERNATIONAL SEARCH REPORT

Inte. ,onal Application No
PCT/GB 99/03472

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/57 A61K7/48 A61K31/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 14472 A (GLAXO GROUP LTD) 3 September 1992 (1992-09-03) example 1 page 2, line 7 claims ---	1,5,18, 21,22
Y	EP 0 042 827 A (AKTIEBOLAGET DRACO) 30 December 1981 (1981-12-30) the whole document --- -/--	1,2, 5-11,14, 18,21,22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 2000	04/02/2000

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INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/GB 99/03472

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	BLEEHEN S.S ET AL.: BRITISH JOURNAL OF DERMATOLOGY, vol. 133, no. 4, - 1995 pages 592-597, XP000864345 page 592, left-hand column, last paragraph page 593, left-hand column, line 33 - line 38 page 594, line 8 - line 18 ---	1,2, 5-11,14, 18,21,22
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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(12) **United States Patent**
Dow et al.

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(45) **Date of Patent: Nov. 27, 2007**

(54) **FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY**

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Related U.S. Application Data

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(52) **U.S. Cl.** **424/484**; 424/485; 424/486; 514/177

(58) **Field of Classification Search** 514/177; 424/484, 485, 486
See application file for complete search history.

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(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

A fluticasone lotion having improved vasoconstrictor and anti-inflammatory activity and higher than expected potency. The fluticasone lotion contains 0.05 weight percent fluticasone propionate and an oil-in-water vehicle that includes excipients. The fluticasone lotion is unexpectedly efficacious while exhibiting an improved safety profile.

19 Claims, No Drawings

FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

This application is a continuation of U.S. Ser. No. 09/830,037 filed 20 Apr. 2001, now abandoned which is a §371 national stage filing of PCT/GB99/03472 filed 20 Oct. 1999.

FIELD OF THE INVENTION

The present invention is generally directed to a lotion comprising fluticasone.

BACKGROUND OF THE INVENTION

Fluticasone propionate is a steroid having anti-inflammatory, anti-pruitic, and vasoconstrictive properties. Fluticasone propionate cream (0.05%) is sold under the tradename CUTIVATE® cream. Each gram of CUTIVATE® cream (0.05%) contains 0.5 mg fluticasone propionate in a base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, buffers and preservatives.

Mineral oil is a known occlusive agent. Occlusion in topical drug delivery is known to increase the vasoconstrictor potency of the topical steroid. By increasing the vasoconstrictor potency, the effectiveness of the steroid is increased. However, occlusive agents such as mineral oil can reduce the aesthetic appeal of topical formulations as they may impart an undesirable oily feel to the skin. By removing or significantly reducing the concentration of the occlusive agent, a decrease in the vasoconstrictor potency of the steroid would be expected. Thus, the effectiveness of the topical steroid formulation would be decreased.

The present fluticasone lotion invention unexpectedly shows increased vasoconstrictor potency of fluticasone at decreased concentrations of occlusive agent, thus increasing the steroid effectiveness. The instant fluticasone lotion also significantly improves the organoleptic feel and spreadability of the drug over a large area as compared to a cream. Specifically, the instant fluticasone lotion has improved vasoconstrictor activity over fluticasone cream formulations. The fluticasone lotion is systemically safe and exhibits significant vasoconstrictor potency and efficacy and excellent anti-inflammatory activity.

SUMMARY OF THE INVENTION

One aspect of the invention is a topical lotion comprising about 0.005 to 1.0 wt. % fluticasone, or a pharmaceutically acceptable salt or ester thereof; a thickening effective concentration of at least one thickener; a conditioning effective concentration of at least one skin conditioning agent; and, an emulsifying effective amount of a surfactant. Unless indicated otherwise herein, all percentages are in terms of weight percent (i.e., w/w, wt. %, etc.). Unless indicated otherwise herein, the term "about" is intended to include values, e.g., weight percents, proximate to the recited range that are equivalent in terms of the functionality of the individual ingredient, the composition or the invention. In addition, unless indicated otherwise herein, a recited range (e.g., weight percents or carbon groups) includes each specific value or identity within the range.

Another aspect of the present invention is a topical fluticasone lotion for the treatment of skin conditions (i.e., dermatological disorders). The lotion comprises about 0.005 to 1.0 wt. % fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to 10.0 wt. % of a C_{14}-C_{20} fatty alcohol, or mixtures thereof; about 1.0 to 5.0 wt. % of at least one skin conditioning agent; about 5.0 to 15.0 wt. % of propylene glycol; up to about 10.0 wt. % mineral oil or soft white paraffin, and the balance being water. The lotion optionally contains additives such as preservatives and buffers.

Another aspect of the invention is a topical fluticasone lotion comprising fluticasone propionate in an amount of from about 0.005 to 1.0 wt. %; a C_{14}-C_{20} fatty alcohol, or mixtures thereof, in an amount of from about 3.0 to 7.0 wt. %; at least one skin conditioning agent in an amount of from about 0.5 to 3.0 wt. %; at least one surfactant in an amount of about 0.25 to 3.0 wt. %; propylene glycol in an amount of from about 7.0 to 12.0 wt. %; up to about 10 wt. % mineral oil or soft white paraffin; and the balance in water, preferably purified water, USP.

Yet another aspect of the invention is a method of treating a skin condition. A skin condition (or dermatological disorder) includes, but is not limited to, corticosteroid-responsive dermatosis, atropic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting and pruritis. The method comprises the steps or acts of providing a lotion including about 0.005 to 1.0 wt. % fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to 10.0 wt. % of a C_{14}-C_{20} fatty alcohol or mixtures thereof; about 1.0 to 5.0 wt. % of one or more skin conditioning agents; about 5.0 to 15.0 wt. % of propylene glycol; up to about 10.0 wt. % of mineral oil or white soft paraffin, and the balance in purified water; and, applying the lotion to the skin having the skin condition. Preferably, the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5. The lotion of the present invention has the added benefit of being chemically and physically stable for at least 6 months at 40° C.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Fluticasone or a pharmaceutically acceptable salt or ester thereof, preferably fluticasone proprionate, is present in the formulation in a concentration of from about 0.005 to 1.0 wt. % preferably 0.005 to 0.5 wt. %, and more preferably about 0.005 to about 0.1 wt. %. The C_{14}-C_{20} fatty alcohol or mixtures thereof are present in the formulation as a thickener and/or stabilizer. Examples include, but are not limited to, cetyl alcohol, stearyl alcohol, and cetostearyl alcohol. The C_{14}-C_{20} fatty alcohol is present in a concentration in the range of from about 1.0 to 10.0 wt. %, preferably about 3.0 to 7.0 wt. %, and more preferably about 4.0 to 6.0 wt. %.

Conventional skin conditioning agents, such as emollient skin conditioning agents, may be present in the lotion of the present invention. Skin conditioning agents are defined in the CTFA (Cosmetic Toiletry and Fragrance Association) Cosmetic Ingredient Handbook (2nd ed. 1992) and the Handbook of Pharmaceutical Excipients (2nd ed. 1994). Preferred examples of such skin conditioning agents include, but are not limited to, cholesterol, glycerine, glycerol monostearate, isopropyl myristate and palmitate, and lanolin alcohols, or mixtures thereof. Particular examples are isopropyl myristate and cetostearyl alcohol. The skin conditioning agent is present in a concentration in the range of from about 1.0 to 5.0 wt. %, preferably about 1.0 to 3.0 wt. %, and more preferably about 1.0 to 2.0 wt. %. In a preferred embodiment, dimethicone is employed in connection with at least one skin conditioning agent. The concentration of dimethicone in the formulation may be up to about

5.0 wt. %, preferably about 0.5 to 3.0 wt. % and more preferably about 1.0 to 2.0 wt. % of the lotion composition.

At least one conventional surfactants may be used in topical formulations to form the oil-in-water emulsion lotion of the present invention. For example, the surfactants may include, but are not limited to, polyoxyalkene oxides of C_{14}-C_{20} fatty alcohols and polyoxyalkylene sorbitan esters, or mixtures thereof. Preferred surfactants include CETOMACROGOL® 1000 (Crodor Inc.), CETETH-20®, TWEEN® 40 or BRIG® 78. The surfactant may be present in a concentration in the range of about 0.25 to 3.0 wt. %, preferably about 0.5 to 2.0 wt. %, and more preferably about 0.75 to 1.5 wt. %.

Optionally, mineral oil or white soft paraffin are incorporated into the lotion in relatively small amounts to act as a skin conditioner. The lotion may also be free of mineral oil and/or white soft paraffin or contain up to about 10.0 wt. %. The lotion may also contain up to about 5.0 wt. % or up to about 2.0 wt. % skin conditioner.

Propylene glycol may be present in the lotion formulation in a concentration of from about 5.0 to 15.0 wt. %, preferably about 7.0 to 12.0 wt. % and more preferably 9.0 to 11.0 wt. %.

The viscosity of the fluticasone lotion may be in the range of about 2,000 to 17,000 centipoise (cps), and preferably about 3,000 to 13,000 cps, as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25° C.

The pH range of the topical fluticasone lotion may be in the range of about 4 to 7. Conventional buffers may be employed in the lotion formulation to achieve the pH range. The buffers include, but are not limited to, sodium citrate/citric acid, dibasic sodium phosphate/citric acid, and the like.

Optionally, conventional preservatives may be used in the present invention. Preferably, preservatives employed in the formulation should pass US Pharmacopoeia, British Pharmacopoeia and European Pharmacopoeia standards. Preferred preservatives include, but are not limited to, imidurea, methylparaben, propylparaben and the like, and combinations thereof.

Treatment of skin conditions with the lotion of the present invention is accomplished by applying the lotion to the affected areas to be treated. The treatment regimen is varied from patient to patient and condition to condition. In general, the fluticasone lotion is to be applied once or twice a day to a treatment area. Preferably, the lotion of the present invention is used to treat atopic dermatitis, inflammatory and pruritic manifestations and corticosteroid-responsive dermatoses.

The lotion of the present invention is manufactured in a conventional manner by mixing the ingredients at elevated temperatures (such as from 45-80° C.) and then cooling the mixture to achieve a smooth, homogeneous oil-in-water emulsion.

The following examples merely illustrate the lotion compositions of the invention and are not to be construed as limiting the scope of the invention. Unless indicated otherwise, all weight percentages are based on the total weight of the composition.

EXAMPLES

Example 1

A topical 0.05 wt. % fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Cetostearyl alcohol, NF	5.00
Isopropyl myristate, NF	1.00
Dimethicone 360, NF	1.00
Cetomacrogol 1000, BP	1.00
Propylene glycol, USP	10.00
Imidurea, NF	0.30
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Citric acid (anhydrous), USP	0.05
Sodium citrate, USP	0.08
Purified water, USP	balance

Example 2

A topical 0.05 wt. % fluticasone propionate lotion formulation in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Cetostearyl alcohol, NF	5.25
Isopropyl myristate, NF	2.00
Propylene glycol, USP	0.00
Ceteth-20	0.75
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Citric Acid (anhydrous)	0.05
Dibasic sodium phosphate	0.06
Purified water, USP	balance

Example 3

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.0
Mineral Oil	3.0
Isopropyl myristate	3.0
Ceteth-20	0.75
Propylene Glycol	0.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 4

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.25

-continued

Ingredient	(wt. %)
Mineral Oil	1.0
Isopropyl myristate	1.0
Ceteth-20	0.75
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 5

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.0
Mineral Oil	10.0
Isopropyl myristate	5.0
Ceteth-20	0.75
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 6

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	7.0
Isopropyl myristate	2.5
Dimethicone	2.5
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 7

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	7.0
Isopropyl myristate	5.0
Dimethicone	2.5
Cetomacrogol 1000	1.0
Propylene Glycol	10.0

-continued

Ingredient	(wt. %)
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 8

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	6.0
Isopropyl myristate	2.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 9

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	4.7
Isopropyl myristate	3.75
Dimethicone	3.75
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 10

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	2.4
Isopropyl myristate	2.5
Dimethicone	5.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 11

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.01
Stearyl Alcohol	5.0
Isopropyl myristate	3.0
Dimethicone	3.0
Ceteth-20	0.75
Propylene Glycol	5.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 12

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.01
Stearyl Alcohol	2.5
Mineral Oil	1.0
Isopropyl myristate	1.0
Dimethicone	1.0
Cetomacrogol 1000	0.5
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 13

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.1
Cetyl Alcohol	7.0
Mineral Oil	2.0
Isopropyl myristate	2.0
Dimethicone	2.0
Cetomacrogol 1000	1.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 14

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.1
Stearyl Alcohol	7.0
Mineral Oil	2.5
Dimethicone	2.5
Ceteth-20	1.0
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 15

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.1
Cetostearyl Alcohol	5.0
Mineral Oil	2.5
Dimethicone	1.0
Tween ® 40	0.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 16

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.1
Stearyl Alcohol	5.25
Mineral Oil	5.0
Brig ® 78	2.0
Propylene Glycol	5.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 17

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetyl Alcohol	2.0
Isopropyl myristate	5.0
Cetomacrogol 1000	0.5

-continued

Ingredient	(wt. %)
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 18

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt. %)
Fluticasone Propionate	0.05
Cetyl Alcohol	2.5
Dimethicone	5.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

The topical anti-inflammatory activity of fluticasone propionate formulations was measured using a vasoconstriction assay (McKenzie and Stoughton, Arch. Dermatol., 86, 608 (1962)).

Approximately 0.1 mL of the drug product of Examples 1-18 were placed on a 2 cm^2 area of the volar aspect of each volunteer's forearm. Application sites were protected with a guard to prevent removal or smearing. The application sites were not occluded. After approximately 16 hours of contact, the protective guards were removed and the sites gently washed and dried.

Skin vasoconstrictor evaluations were preformed on a 4 point scale (0 [no blanching]-3[marked blanching]) at time points corresponding to 2, 3, 6, 8, and 24 hours after drug removal. The data were used to calculate the mean blanching response and the area under the curve (AUC) for the blanching versus time. The higher the score, mean or area under the curve (AUC), the more topically potent. The results are tabulated in Table 1.

TABLE 1

Measure*	Lotion Example 1	Lotion Example 2	CUTIVATE ® (Fluticasone proprionate) Cream Comparative Example
AUC	28.4	26.7	21.4
Mean	1.58	1.49	1.22

*Results from 17 volunteers.

The fluticasone lotions of the present invention show higher vasoconstriction scores than fluticasone cream. As shown by the 17 patient data set, the vasoconstriction potency of the fluticasone lotions is greater than the cream.

The fluticasone lotion of the present invention has proven to be unexpectedly superior in terms of efficacy and safety. Evaluations were performed using the Vasoconstrictor Assay. Evaluations also used a human model to predict clinical potency of corticosteroids in (1) controlled efficacy and safety trials and (2) subjects with a corticosteroid-responsive dermatosis, atopic dermatitis. Safety and efficacy evaluations were performed on the fluticasone lotion 0.05% by applying the lotion extensively to all body regions: head and neck (including face), trunk, upper limbs and lower limbs.

The potency of the fluticasone lotion, as determined by the Vasoconstrictor Assay, was greater than mid-potency fluticasone cream (CUTIVATE™ Cream). The potency of the fluticasone lotion was less than the high-potency corticosteroid preparations. Application of the lotion formulation over 4 weeks resulted in a superior adverse event profile devoid of commonly encountered side effects encountered using corticosteroids in the mid-to-high potency range.

The instant fluticasone lotion was assessed in view of projected efficacy outcomes from the Vasoconstrictor Assay (VC Assay) in humans and corroborated by efficacy outcomes in multicenter vehicle-controlled clinical trials. It was highly desirable for the lotion formulation to show both systemic (adrenal axis suppression) and local (atrophogenic) responses to corticosteroids. The fluticasone lotion was unexpectedly superior in both categories, and particularly superior in that no atrophy was observed (based on associated signs) even in the more susceptible region (i.e., the face, head and neck).

The Vasoconstrictor Assay (VC Assay; McKenzie and Stoughton) is a standard dermatological assay used to predict the potency of corticosteroid formulations. Potency is related to both side effect potential and efficacy in the treatment of mild to severe dermatoses. Reactions of particular concern include skin thinning (atrophy, including telangectasia), and adrenal axis suppression, which can occur more often (1) under occlusions or (2) when higher potency corticosteroids are employed.

In the VC assay, fluticasone lotion 0.05% was compared to low-potency (HYTONE™ Lotion), mid-potency (CUTIVATE™ Cream; and fluticasone cream 0.05%) and high-potency (TEMOVATE™ Cream; ELOCON™ Lotion). Potency was estimated for two subject populations (Intent to Treat and Positive responders) and includes 3 outcome assessments: 2-hour mean blanching score, are under the time-blanching score curve (AUC) and Average mean blanching from 5 timepoints. The results from the "responder" population is summarised in Table 2.

TABLE 2

		Responder Population		
Treatment	Potency	2 hour score	AUC	Avg. mean blanching
TEMOVATE ™	High	2.7	36.6	2.0
ELOCON ™	High	2.2	33.4	1.8
Fluticasone lotion (0.05%)	Mid to High	2.1	26.7	1.5
CUTIVATE ™ Cream	Mid	1.8	21.4	1.2
HYTONE ™ Lotion	Low	0.8	9.5	0.6

The results show that the fluticasone lotion of the present invention has an unexpectedly high potency for a lotion-based composition.

In addition, as shown in Table 3, criticality for the presence of fluticasone in the lotion of the present invention was established by the comparison between applying the vehicle alone (the fluticasone lotion minus the fluticasone propionate) and the fluticasone lotion. The FPL10005,

FPL3003 and FPL30004 studies used the following fluticasone 0.05% lotion formulation.

Ingredient	(wt. %)
fluticasone propionate (micronized)	0.05
cetostearyl alcohol, NF	5.0
isopropyl myristate, NF	1.0
dimethicone 360, NF	1.0
polyoxyethylene (20) cetostearyl ether, NF	1.0
propylene glycol, USP	10.0
imidurea, NF	0.14
methylparaben, NF	0.17
propylparaben, NF	0.06
citric acid (hydrous), USP	0.05
sodium citrate, USP	0.08
purified water, USP	balance (also QSAD)

TABLE 3

Study	Diagnosis	Application	No. subjects	Outcome Good to cleared (%)
FPL30003	Atopic Dermatitis	QD for up to 4 weeks	FPL (110) Veh. (110)	FPL (78%)* Veh. (33%)
FPL30004	Atopic Dermatitis	QD for up to 4 weeks	FPL (111) Veh. (107)	FPL (68%)* Veh. (28%)

*subjects showing >50% clearing of lesions
"Veh." is vehicle only formulation

The data of Table 3 show that the fluticasone lotion is more than twice as effective as the vehicle. In a once-a-day application, the differences (%) between the vehicle-only and the fluticasone lotion are 40% and 45% (FPL30004 and FPL30003, respectively). The advantage of the fluticasone propionate lotion over the vehicle control was unexpectedly superior. It is worth noting that the fluticasone lotion application rate was half the preferred application rate of twice per day.

Systemic safety of fluticasone lotion (study FPL10005) was assessed utilising the measurement of adrenal responsiveness to a challenge of cosyntropin ($ACTH_{1-29}$) and measuring the plasma levels of cortisol both before and 30 minutes after ACTH challenge. HPA axis was considered suppressed if the cortisol response to the challenge was less than 18 ug/dL. These studies were conducted in paediatric populations from 3 months to 5 years of age. Because children have a high ratio of body mass to surface, that population is considered to be more at risk than adults.

In these studies fluticasone formulations were tested following a 3 or 4 week course of twice daily application of the fluticasone lotion to at least 35% of the body surface area in subjects with moderate to severe eczema. The results are summarised in Table 4.

TABLE 4

Cortisol responses - plasma levels = 18 ug/dL indicate suppression

Study	Preparation	Adrenal Responsiveness, # suppressed/total
FPL10005	Lotion	0/42

These data show that the fluticasone lotion did not suppress the adrenal responsiveness to ACTH stimulation. CUTIVATE™ lotion produced low adrenal suppression as evaluated by the cosyntropin ($ACTH_{1-29}$) stimulation test in paediatric subjects. This age group would be expected to be the most susceptible to side effects of corticosteroids. No adrenal suppression was noted for CUTIVATE™ lotion. These results were unexpectedly superior based on potency estimates from the VC Assay.

Treating skin diseases with topical corticosteroids is of particular concern where the skin is thin (e.g., the face) due to the potential atrophy side effect. Skin atrophy and atrophy-associated signs (such as telangectasia) were monitored in safety studies (HPA Axis Suppression) and efficacy (multicenter pivotal trials). The fluticasone lotion showed no atrophy-associated changes (see Table 4). In addition, atrophogenic potential was assessed in two large multicenter trials (FPL30003, N=110 treated with fluticasone); FPL30004; N=111 treated with fluticasone). The subjects had moderate-to-severe atopic dermatitis. After once daily administration for up to 4 weeks, no atrophy or associated signs were ascribed to drug treatment.

Based on the observed outcomes in the VC Assay (used to predict clinical potency), it was expected (1) that the therapeutic benefit would be only slightly more than that for CUTIVATE™ Cream and (2) that the side effects would reflect those observed for CUTIVATE™ Cream. The results were unexpected in that the lotion formulation was more effective than, and superior to, the cream. At half the application rate of fluticasone lotion, a lack of side effects were observed. That observation was unexpected since application of steroids of similar potency typically cause some side effects. As noted herein for the lotion, the lack of both systemic (HPA Axis suppression) and local side effects, even to sensitive areas such as the face (head and neck region) was unexpected.

It will be apparent to those skilled in the art that many modifications and equivalents thereof may be made without departing from the spirit and scope of the invention as set forth in the appended claims.

We claim:

1. A topical lotion, comprising:
about 0.005 to 1.0 wt. % fluticasone, or a pharmaceutically acceptable salt or ester thereof;
about 4.0 to 6.0 wt. % of a C_{14}-C_{20} fatty alcohol or mixtures thereof;
about 1.0 to 5.0 wt. % of at least one first skin conditioning agent;
about 5.0 to 15.0 wt. % propylene glycol; and
the balance in water;
wherein the lotion is free of mineral oil and white soft paraffin, and
wherein the lotion causes more vasoconstriction when applied to living human skin than does application of a cream containing mineral oil or soft white paraffin, or both, the cream containing the same amount of the fluticasone or the pharmaceutically acceptable salt or ester thereof.

2. The lotion of claim **1** further comprising about 0.25 to 3.0 wt. % of at least one surfactant.

3. The lotion of claim **1** further comprising about 0.5 to 2.0 wt. % of at least one surfactant.

4. The lotion of claim **1** further comprising dimethicone in an amount up to about 5.0 wt. %.

5. The lotion of claim **4** further comprising about 0.5 to 3.0 wt. % of dimethicone.

6. The lotion of claim **4** further comprising about 1.0 to 2.0 wt. % of dimethicone.

7. The lotion of claim **5** wherein said C_{14}-C_{20} fatty alcohol or mixtures thereof is cetostearyl alcohol.

8. The lotion of claim 7 wherein said first skin conditioning agent is isopropyl myristate.

9. The lotion of claim 8 further comprising about 0.25 to 3.0 wt. % of at least one surfactant.

10. The lotion of claim 8 further comprising about 0.5 to 2.0 wt. % of at least one surfactant.

11. The lotion of claim 10 wherein said surfactant is Cetomacrogol.

12. The lotion of claim 11 further comprising one or more buffers.

13. The lotion of claim 12 further comprising one or more preservatives.

14. The lotion of claim 13 wherein said fluticasone, or a pharmaceutically acceptable salt or ester thereof is fluticasone propionate.

15. The lotion of claim 14 wherein said one or more buffer is selected from the group consisting of: sodium citrate and citric acid.

16. The lotion of claim 15 wherein said one or more preservative is selected from the group consisting of: imidurea, methylparaben, and propylparaben.

17. A method of treating a skin condition treatable by fluticasone, comprising topically administering to a patient in need thereof a lotion according to claim 14.

18. The method of claim 15 wherein said skin condition is selected from the group consisting of: corticosteroid-responsive dermatosis, atopic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting and pruritis.

19. A topical lotion, comprising:

about 0.05 wt. % fluticasone, or a pharmaceutically acceptable salt or ester thereof;

about 4.0 to 6.0 wt. % of cetostearyl alcohol;

about 1.0 to 2.0 wt. % of isopropyl myristate;

about 5.0 to 15.0 wt. % propylene glycol;

about 0.5 to 3.0 wt. % of dimethicone;

about 0.25 to 3.0 wt. % of at least one surfactant; and

the balance in water;

wherein the lotion is free of mineral oil and white soft paraffin, and

wherein the lotion causes more vasoconstriction when applied to living human skin than does application of a cream containing mineral oil or soft white paraffin, or both, the cream containing the same amount of the fluticasone or the pharmaceutically acceptable salt or ester thereof.

* * * * *

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Title

Fluticasone lotion having improved vasoconstrictor activity

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